REMARKS

The present invention relates to the use of bone marrow stromal cells to rescue a mammal from a lethal dose of total body irradiation.

Applicants appreciate the time taken by the Examiner and the Primary Examiner during the telephone interview that took place on August 11, 2004, with Applicants' representative, Kathryn Doyle (the undersigned). During the telephone interview, Applicants agreed to amend the claims to identify the bone marrow stromal cells of the present invention as primary cultured cells, and to add a new set of claims to recite that the cells are administered immediately upon isolation or following *in vitro* culturing for no more than the third passage. By way of the present Amendment, Applicants have amended the claims accordingly, as more fully set forth below.

Claims 1-32 are pending and under consideration in the present application following entry of the present Amendment. Claims 1, 5, 9, 13-16 have been amended and claims 17-32 have been added herein. Support for the amendments to claims 1, 5, 9, 13-16 and the addition of new claims 17-32 is found in the as-filed specification as detailed below and, therefore, no new matter has been added by way of these amendments and additions.

Supplemental Information Disclosure Statement

Applicants submit herewith a Supplemental Information Disclosure Statement and the attached Form PTO-1449. It is requested that the enclosed references listed on the Form PTO-1449 be considered by the Examiner and be made of record. Applicants respectfully request that the Examiner return to the undersigned an initialized copy of the Form 1449 at the Examiner's earliest convenience.

Support for amendments to claims 1, 5, 9, 13-16 and new claims 17-32

During the telephone interview dated August 13, 2004, Applicants agreed to amend the claims to have the claims recite primary cultured cells, and to add a new set of claims to recite that the cells are cultured *in vitro* for no more than the third passage.

Applicants assert that the as-filed specification amply supports the amendment to the claims with respect to the term primary cultured cells, and as such does not add new matter. Although the term "primary" is not explicitly recited in the as-filed specification, one skilled in

the art would be able to infer, based upon the disclosure of the instant application, that the cells of the present invention are primary cultured cells.

As set forth in MPEP §2163, "While there is no *in haec verba* requirement, newly added claim limitations must be supported in specification through express, implicit, or inherent disclosure." Applicants respectfully argue that the specification more than adequately supports a primary cultured cell. The as-filed specification describes a method of culturing a mixed population of bone marrow cells, containing both adherent and non-adherent cells, isolated from an allogeneic donor, wherein the population of adherent cells are separated from non-adherent cells. The adherent population of cells, which are referred to by the specification as bone marrow stromal cells, are cultured for a period of time prior to the administration to an irradiated mammal. Nowhere does the specification disclose that the bone marrow stromal cells of the present invention are cultured in a manner that would transform or immortalize the cells. Therefore, it can be inferred based upon the as-filed specification that the cells of the present invention are primary cultured cells because the cells of the present invention are not manipulated in a manner that would produce a transformed/immortalized cell. One could not arrive at a transformed/immortalized cell using the methods disclosed in the specification. For example on page 9 of the specification, it is disclosed that the bone marrow stromal cells are administered to a mammal upon isolation or following a period of *in vitro* culturing. Further, the specification beginning on page 15 discloses that the isolated bone marrow stromal cells are cultured *in vitro* prior to transplantation into a mammal. Applicants point out that the specification does not discuss any further manipulation of the cells outside the standard method of culturing and expanding the cells by passing the cells *in vitro* prior to administering the cells to an irradiated mammal. Moreover, the specification does not provide any information as to how one skilled in the art would be able to arrive at a transformed/immortalized cell.

In addition to the amendments to claims 1, 5, 9 and 13-16, with respect to characterizing the bone marrow stromal cells as primary cultured cells, Applicants have added claims 17-32, which are similar to claims 1-16, except claims 17-32 recite that the cells are cultured *in vitro* for no more than the third passage. New claims 17-32 are amply supported by the specification, and as such do not add new matter. For example, on page 15, lines 12-13, it is stated in the specification that "the cells used for transplantation were allowed to reach third passage." Further, on page 15, beginning on line 18, the specification recites "MSC grown to

third passage in culture." As such, these amendments to the claims are supported by the specification, and no new matter has been added.

Rejection of claims 1, 2, 4-6, 8-10 and 12-16 pursuant to 35 U.S.C. § 102(b)

In the Office Action dated May 19, 2004, the Examiner maintained his rejection of claims 1, 2, 4-6, 8-10 and 12-16 under U.S.C. § 102(b) as being anticipated by Anklesaria et al. (1987, Proc. Natl. Acad. Sci., USA 84:7681-85). Specifically, the Examiner opines that Anklesaria teaches engraftment of a clonal bone marrow stromal cell line *in vivo* to stimulate hematopoetic recovery from total body irradiation, thereby anticipating the present invention. Applicants respectfully traverse this rejection for the following reasons.

It is well settled that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP §2131 (quoting *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)). "The identical invention must be shown in as complete detail as is contained in the . . . claim." *Id.* (quoting *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Therefore, Anklesaria must describe each and every element of claims 1, 2, 4-6, 8-10 and 12-16, in order to anticipate these claims under 35 U.S.C. § 102(b), and this reference does not.

Anklesaria does not anticipate the present invention because the reference does not teach the cells of the present invention as encompassed by the amended claims and supported in the as-filed specification. Anklesaria teaches a stable clonal cell line (GB1/6) which was established from the adherent layer of long-term marrow cultures from B6Cast mice. Anklesaria begins with a transformed/immortalized cell line (GB1/6), which is then selected for resistance to neomycin by culturing in the presence of G418. A subclone of these cells was then isolated and administered to a mouse that had undergone total body irradiation to stimulate hematopoietic recovery in the mouse. Thus, this reference teaches that one can begin with a transformed/immortalized cell line, develop a subclone thereof, and administer the cells of the subclone to a mammal for the purpose of rescuing the mammal from total body irradiation.

Applicants instead use isolated bone marrow stromal cells that are primary cultured cells, wherein the cells are administered to an irradiated mammal before the cells have been rendered transformed or immortalized. As supported by the as-filed specification and

encompassed by the amended claims, the cells of the present invention are not transformed/immortalized. Rather, the cells of the present invention are primary cultured cells, including cells that have been cultured for no more than the third passage.

In fact, Anklesaria solely uses a transformed/immortalized cell line for the administration into a mammal for the purpose of rescuing the mammal from total body irradiation. The claims, as amended and newly added claims 17-32 herein, recite primary cultured cells and cells cultured *in vitro* for no more than the third passage, and therefore are distinct from the cells of Anklesaria. The cited reference does not disclose primary cultured cells or cells that are cultured for no more than the third passage, and therefore cannot anticipate the present invention.

Further, Applicants point out that the cells of Anklesaria relate to a subclone which is a pure population that has been isolated from a colony resistant to G418 and thereby rendered homogeneous in nature. However, the cells of the present invention, as encompassed in the claims and defined by the specification, are a mixture of adherent cells that have been separated from a mixed population of adherent and non-adherent cells derived from bone marrow of an allogeneic donor. The present invention does not require that the cells are cultured in a manner that would generate a pure population of bone marrow stromal cells. Rather, the invention relates to the discovery that bone marrow cells can be isolated from an allogeneic donor, and with minimum culturing without establishing a homogeneous transformed/immortalized cell line, can be administered to a mammal for a therapeutic effect. Anklesaria does not disclose using such a population of cells to rescue a mammal from total body irradiation. In fact, Anklesaria teaches away from the present invention because Anklesaria uses transformed/immortalized cells that have been cultured for an extensive period of time and manipulated in a manner that arrives at a clonal cell line that is homogenous in nature.

Accordingly, Applicants request that the rejection of claims 1, 2, 4-6, 8-10 and 12-16 under U.S.C. § 102(b) be reconsidered and withdrawn upon entry of the present Amendment for the reasons set forth elsewhere herein. Further, Applicants respectfully submit that new claims 17-32, which relate to a population of human bone marrow stromal cells cultured *in vitro* for no more than the third passage, are in condition for allowance because such a population of cells would not be a homogeneous transformed/immortalized cell line as disclosed in Anklesaria.

Rejection of Claims 3, 7 and 11 pursuant to 35 U.S.C. §103(a)

The Examiner has maintained his rejection of claims 3, 7 and 11 pursuant to 35 U.S.C. § 103(a), as being obvious over Anklesaria et al., and in further view of Palsson et al. (U.S. Patent No. 5,635,386). Specifically, the Examiner contends that Palsson teaches the use of human hematopoietic stem cells and their cultures that "afford improved methods for bone marrow transplantation," and the combination of the teachings of Anklesaria with Palsson would arrive at the present invention. Applicants respectfully traverse this rejection for the following reasons.

The three-prong test must be met for a reference or a combination of references to establish a *prima facie* case of obviousness, and this criteria has not been satisfied in the instant matter. The MPEP states, in relevant part:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. MPEP § 2142.

None of these criteria have been met here.

The present invention encompasses a method of rescuing a mammal from a lethal dose of total body irradiation, said method comprising administering primary cultured bone marrow stromal cells to an irradiated mammal, thereby rescuing said mammal from a lethal dose of total body irradiation. Neither Anklesaria nor Palsson suggest to or motivate the skilled artisan to arrive at the present invention as encompassed in the amended claims and defined by the specification.

Applicants argue that Anklesaria offers no suggestion or motivation to modify the reference or to combine reference teachings to arrive at the present invention. Even if Anklesaria did in some way, which it does not, offer a suggestion or motivation to combine the references, Applicants contend that the combined teachings would teach away from the present invention. As discussed elsewhere herein, Anklesaria teaches a transformed stable clonal cell line (GB1/6) which was established from the adherent layer of long-term marrow cultures from B6Cast mice and made resistant to neomycin. As such, Anklesaria does not teach Applicants' cells, which are

primary cultured cells or cells that have been cultured for no more than the third passage. Nowhere does Anklesaria offer a suggestion or motivation to use Applicants' cells for rescuing a mammal from total body irradiation.

The combination of Anklesaria with Palsson does not render the present invention obvious. As an initial matter, Applicants contend that the teachings of Palsson do not correct the deficiencies of Anklesaria. Similar to Anklesaria, Palsson does not teach a primary cultured bone marrow stromal cell or a bone marrow stromal cell that has been cultured *in vitro* for no more than the third passage. Rather, Palsson teaches the use of human hematopoietic stem cells. Palsson does not mention the use of isolated primary cultured bone marrow stromal cells or cells that have been cultured *in vitro* for no more than the third passage, for the administration to a mammal for the purpose of rescuing a mammal from total body irradiation.

Furthermore, Applicants assert that Palsson teaches the culturing of hematopoietic stem cells in the presence of bone marrow stromal cells *in vitro* to enhance the production of a hematopoietic cell. The co-culturing of the hematopoietic stem cells with the bone marrow stromal cells helps in the maturation of the hematopoietic stem cells into cells of the hematopoietic lineage. Palsson teaches a cell culture media comprising hematopoietic stem cells and bone marrow stromal cells, wherein the hematopoietic stem cells are in contact with the bone marrow stromal cells in order for the hematopoietic stem cells to receive any benefit from the bone marrow stromal cells. However, the present invention teaches that the hematopoietic reconstitution is an endogenous phenomenon without the requirement of having the hematopoietic stem cells be in contact with the bone marrow stromal cells. In fact, Palsson teaches away from the present invention because Palsson teaches the co-culturing of both hematopoietic stem cells and bone marrow stromal cells, and that the two cells are required to contact one another in order for the maturation of the hematopoietic stem cell. Therefore, not only does Palsson not teach the cells of the present invention, but Palsson does not even teach administering the cells to an irradiated mammal for the purpose of rescuing an animal from total body irradiation. Accordingly, Palsson, even in view of Anklesaria fails to offer a suggestion or motivation to modify the reference(s) to arrive at the instant invention.

The second criteria for establishing a *prima facie* case of obviousness is that there must be a reasonable expectation of success. Anklesaria describes the use of a stable clonal stromal cell line, which was made resistant to neomycin, in the stimulation of hematopoietic

skilled artisan would not have any reason to expect that isolated primary cultures of bone marrow stromal cells or bone marrow stromal cells that have been cultured *in vitro* for no more than the third passage, would rescue a mammal from a lethal dose of total body irradiation. Rather, upon reading Anklesaria, a skilled artisan would only have a reasonable expectation of success for using a pure population of transformed/immortalized cultures. From this, one skilled in the art would have no reason to expect success in rescuing a mammal from a lethal dose of body irradiation by administrating to the mammal a population of primary cultured bone marrow stromal cells that has not been cultured to generate a pure clonal cell line, and that has not been rendered transformed/immortalized. Therefore, Anklesaria fails to render the present invention *prima facie* obvious because Anklesaria offers no reason that using a primary cultured cell or a cell that has been cultured *in vitro* for no more than the third passage would rescue a mammal from a lethal dose of body irradiation.

In addition, Palsson, when combined with the teachings of Anklesaria does not generate a reasonable expectation of success in rescuing a mammal from total body irradiation by administering a mammal with primary cultured bone marrow stromal cells or bone marrow stromal cells that have been cultured *in vitro* for no more than the third passage. As discussed elsewhere herein, Palsson teaches co-culturing hematopoietic stem cells with bone marrow stromal cells, and Anklesaria teaches a transformed/immortalized cell line made resistant to neomycin. One skilled in the art would have no reasonable expectation of success in combining the teaching of the two references to arrive at the present invention, wherein the cells are cultured with minimal manipulation prior to the administration to the mammal in need thereof. At best, the combination of Anklesaria and Palsson provides a reasonable expectation of success using a transformed/immortalized cell line that has been cultured extensively and made to be homogeneous in nature prior to the administration of the cells to the mammal in order to provide a therapeutic benefit. The combination of the references does not provide a reasonable expectation of success using the cells of the present invention for rescuing a mammal from total body irradiation.

The third prong in establishing a *prima facie* case of obviousness requires the prior art reference or references to teach or suggest all of the claim limitations. As discussed elsewhere herein, Anklesaria does not teach the cells of the present invention as encompassed by the claims and defined by the specification. Therefore, Anklesaria does not teach or suggest all

the claims and defined by the specification. Therefore, Anklesaria does not teach or suggest all embodiments of the claims. In addition, the teachings of Palsson, as discussed elsewhere herein are unable to correct the deficiencies of Anklesaria, and therefore, Anklesaria in view of Palsson, cannot render the present invention *prima facie* obvious. In fact, the combination of these references would teach away from the present invention because Anklesaria teaches using a different cell than Applicant's cell and Palsson teaches co-culturing hematopoietic stem cells with bone marrow stromal cells to rescue a mammal from total body irradiation. Accordingly, Applicants respectfully request reconsideration and withdrawal of the Examiner's rejection pursuant to 35 U.S.C. §103(a).

Summary

Applicants respectfully submit that each rejection of the Examiner to the claims of the present application has been overcome or is now inapplicable, and that claims 1-16 and new claims 17-32 are now in condition for allowance. Reconsideration and allowance of these claims is respectfully requested at the earliest possible date.

Respectfully submitted,

DARWIN J. PROCKOP *ET AL.*

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(Date)

By: _____

KATHRYN DOYLE
Registration No. 36,317
MORGAN, LEWIS & BOCKIUS, LLP
1701 Market Street
Philadelphia, PA 19103-2921
Telephone: (215) 963-5000
Direct Dial: (215) 963-4723
Facsimile: (877) 432-5001
E-Mail: kdoyle@morganlewis.com
Attorney for Applicants

KD/QDN